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Synthesis and relative bioavailability of meptazinol benzoyl esters as prodrugs

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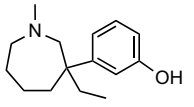
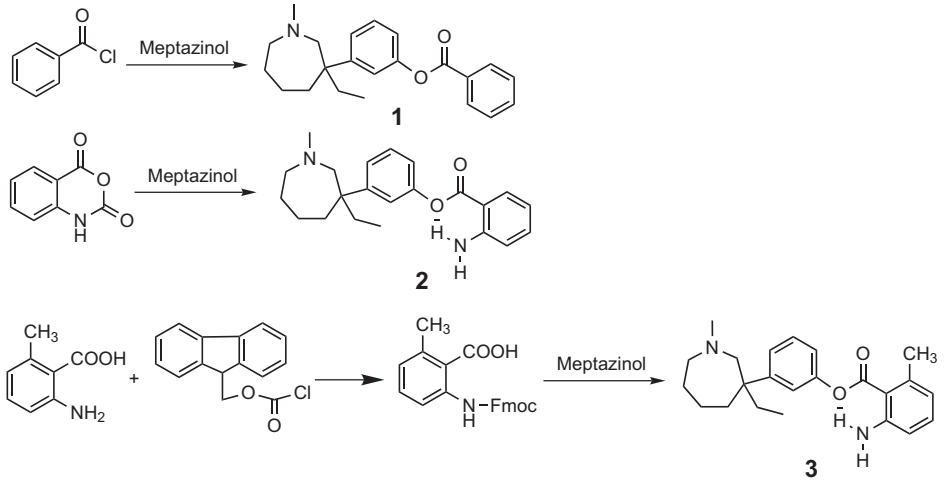
Abstract—Three meptazinol benzoyl esters (**1**–**3**) were synthesized as prodrugs to minimize the first-pass effect of meptazinol and improve the bioavailability. Among these three esters, compound **3** showed better bioavailability than the parent meptazinol. Further, the relative regional bioavailability of prodrug **3** was evaluated using in situ closed loop study in rats, which showed that prodrug **3** has higher absorption efficacy in rat intestine. Thusly, prodrug **3** may be worth for further development.

Known as a partial opioid agonist, meptazinol (3-(3-ethylhexahydro-1-methyl-1*H*-azepin-3-yl) phenol) was used clinically for short-term relief of moderate to severe pain (e.g., the pain of childbirth, injury or surgery). Unlike other typical opiates such as morphine and fentanyl, it accompanies less respiratory depression and addictive potential. Meptazinol was commercially available since 1989 and embodied in British Pharmacopoeia in 1998. New clinical applications, pharmacophores, and analgesic mechanism of meptazinol were reported recently[1–6] both from our group and other researchers.



Meptazinol

However, meptazinol displayed poor oral bioavailability (8.69%) because of serious first-pass effect in liver similar



Scheme 1. Synthetic route to the target compounds.

Keywords: Meptazinol; Prodrug; Benzoic ester; Analgesic.
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Table 1. Analgesic activity of objective compounds

Sample	Analgesic activity		
	Hot-plate test	Acetylcholine induced mice writhing test	
	Ip 100 μmol/kg	Ig 50 μmol/kg	
		After 40 min	After 80 min
Meptazinol[a]	5/10	4/10	1/10
1	4/10	2/10	2/10
2	3/10	1/10	0/10

[a] Testified as the control.

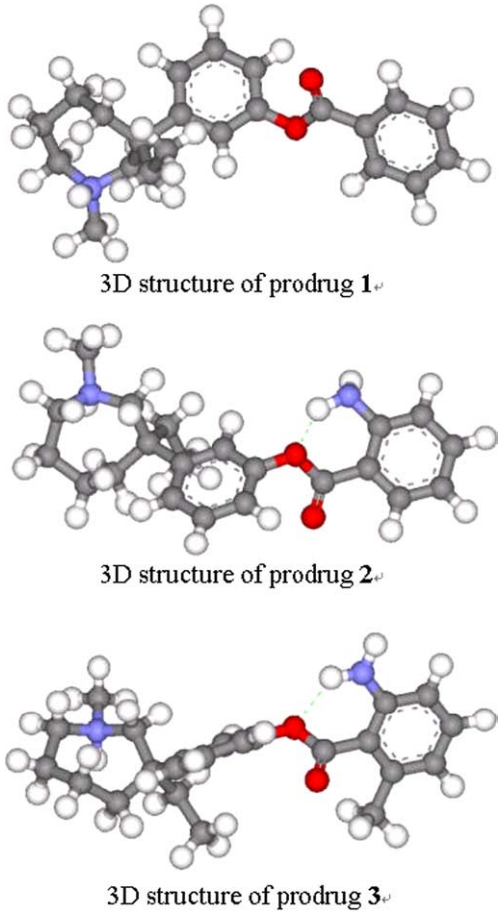

Figure 1. 3D structure models of three prodrugs.

to other opiates with a phenol group.[7] Furthermore, good correlation between meptazinol analgesic potency and plasma concentration was observed by Franklin et al.[8] Thusly, masking of this phenol group with esters could protect this drug from enzyme metabolism, and enhance hydrophobicity as well to improve its pharmacokinetic properties. In the present study, three benzoyl ester derivatives (prodrugs **1**–**3**) of meptazinol were prepared to improve its relative bioavailability and reduce the first-pass effect.

As outlined in Scheme 1, **1** and **2** were prepared simply by condensing meptazinol with benzoic chloride and isatoic anhydride, with 58% and 22% yield, respectively. Protection of the amine group of (2-amine-6-methyl) benzoic acid with 9-fluorenylmethoxycarbonyl chloride (Fmoc-Cl) followed by coupling with meptazinol in the presence of dicyclohexylcarbodiimide (DCC) and 4-dimethylaminopyridine (DMAP) gave meptazinol (2′-amine-6′-methyl) benzoyl ester (prodrug **3**) in about 64% yield.[9] We chose Fmoc as a protecting group simply because it has been widely used as an amine protective group in many coupling reactions in peptide related chemistry. The structures of these prodrugs and their hydrochloride salts were determined by ^{1}H NMR, MS, and HRESI.

Prodrugs **1** and **2** hydrochlorides were administrated by intraperitoneal and intragastric administration to Kunming white mice. The analgesic potency was determined by hot-plate and acetylcholine induced mice writhing assays (Table 1). However, both prodrugs showed similar analgesic potency and duration with that of meptazinol. A possible explanation was that these esters were easy to hydrolyze in acidic circumstance of the stomach.

Given this consideration, (2-amine-6-methyl)-benzoic acid meptazinol ester (prodrug **3**) was further designed and prepared. As shown in the 3D molecular modeling structures using SYBYL 6.9 (Tripos Inc., 1699 South Handley Rd, Suite 303, St. Louis, MO 63144) (Fig. 1), the carbonyl group of prodrug **3** is surrounded by both the 2′-amino group and the 6′-methyl group which could thusly protect the ester bond from hydrolysis.

It is interesting to note that unlike other two meptazinol prodrugs (compounds **1** and **2**), prodrug **3** showed significant improvement in bioavailability assays comparing to the parent meptazinol (Table 2).[10] Since good correlation between meptazinol analgesic potency and plasma concentration was observed by Franklin et al.,[10] it was of considerable interest to further investigate prodrug **3**'s specific regions absorption in intestine and local metabolism. The results were displayed in Table 3 and Figure 2. Prodrug **3** showed significant increase in looped duodenum, jejunum, and colon absorption than the control. Especially it showed more than 10-fold absorption in duodenum than meptazinol.

Table 2. Relative bioavailability of prodrugs **1**–**3**

	F (%)								*P*[a]
	1	2	3	4	5	6	Mean	SD	
Prodrug **1**	58.07	53.89	111.90	81.61	75.38	133.23	85.68	24.59	0.1206
Prodrug **2**	101.04	183.64	106.71	81.90	59.82	80.36	102.25	28.62	0.6150
Prodrug **3**	174.27	120.08	135.88	167.97	129.94	149.21	146.22	21.56	0.0021

[a] Statistical *P* value. $P > 0.05$, no statistical significance. $P < 0.01$, statistical significance.

Table 3. Relative bioavailability of prodrug **3** hydrochloride into closed loop stomach, duodenum, jejunum or colon of each rat

Looped part	*F* (%)					
	No. 1	No. 2	No. 3	No. 4	Mean	SD
Stomach	50.12	48.37	60.28	107.65	65.40	27.86
Duodenum	1398.26	784.24	917.96	867.84	1024.39	276.35
Jejunum	612.21	510.72	552.41	522.16	562.72	45.43
Colon	459.70	511.29	528.46	654.05	541.45	82.47

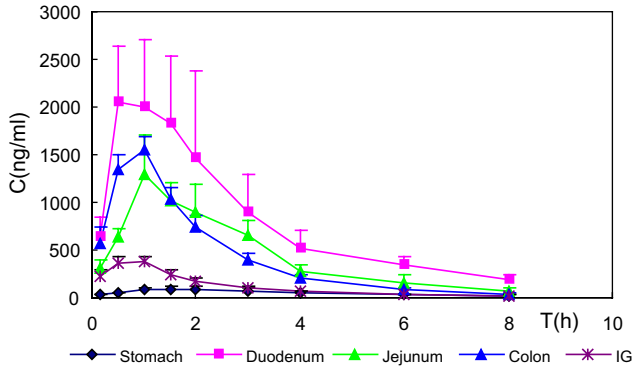

Figure 2. Mean plasma meptazinol concentration after intra-stomach, intra-duodenum, intra-jejunum, intra-colon administration of prodrug **3** at a dose of 92.8 μmol/kg.

In conclusion, we have synthesized three meptazinol benzoyl esters as prodrugs to minimize the first-pass effect of meptazinol and to enhance the bioavailability. Among the three prodrugs (**1**–**3**) that we prepared, prodrug **3** showed much higher absorption efficacy in rat intestine comparing to meptazinol which correlated well with its enhanced bioavailability. Thusly, it may be worth for further development.

Acknowledgements

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9. Spectral data of the selected compound. Prodrug **3** hydrochloride: ^{1}HNMR (400 Hz, DMSO) δ 9.88 (br s, ≈1/2 H, NH^+), 8.60 (br s, ≈1/2H, NH^+), 7.50–7.42 (m, 1H, Ar-H), 7.33–7.09 (m, 4H, Ar-H), 6.69 (d, 1H, Ar-H), 6.50–6.47 (m, 1H, Ar-H), 4.01–3.97 (m, 1H, N-CH), 3.87 (br s, NH_3^+), 3.62–3.58 (m, 1H, N-CH), 3.46–3.41 (q, 2H, CH_2CH_3, J = 7.0), 3.18–3.14 (m, 2H, N-CH_2), 2.86 (d, 3H, N-CH_3, J = 3.5), 2.47 (s, 3H, Ar-CH_3), 1.84–1.46 (m, 4H, $CH_2 \times 2$), 1.05 (t, 2H, CH_2, J = 7.0 Hz), 0.56 (t, 3H, CH_2CH_3, J = 7.3 Hz); ES-MS (*m*/*z*, M^+) 366; HRMS (ESI, M+1) calcd for $C_{23}H_{31}N_2O_2$: 367.2380. Found 367.2381.
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